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Title: Patient Empowered Strategy to Reduce Asthma Morbidity in Highly Impacted Populations; PeRson EmPowered Asthma REIief (PREPARE)

Date: 3/5/2018

Answer all questions accurately and completely in order to provide the PHRC with the relevant information to assess the risk-benefit ratio for the study. Do not leave sections blank.

PRINCIPAL/OVERALL INVESTIGATOR
Elliot Israel, MD

PROTOCOL TITLE
Patient Empowered Strategy to Reduce Asthma Morbidity in Highly Impacted Populations (PREPARE)

FUNDING
Patient Centered Outcomes Research Institute (PCORI)

VERSION DATE
February 20, 2018

SPECIFIC AIMS

Concisely state the objectives of the study and the hypothesis being tested.

VANGUARD (4 initial sites):

1) To determine whether our study operations and processes are functional.

   These operations and processes include the enrollment process for sites and for study participants, our communication with patients and with physicians (which include written communication, teleprompt response system, web system via mobile and desktop), our drug delivery system, and the Propeller system.

2) To determine what are our barriers to study implementation.

3) To determine whether patients understand what we mean to communicate to them.

There is no hypothesis for the Vanguard portion, we are testing the process and asking for feedback from the patients.

FULL STUDY:
We will **not** be testing the study logistics as in the Vanguard, we will be conducting the study based on the hypothesis below.

1: To assess whether a Patient Activated, Reliever-Triggered Inhaled CorticoSteroid (PARTICS) strategy can reduce asthma morbidity.

2: To examine whether the effectiveness of a Patient Activated, Reliever-Triggered ICS (PARTICS) strategy differs between African American or Hispanic/Latino adults or by smoking status.

Exploratory Aim: To examine, whether particular patient clinical characteristics (e.g. prior exacerbations) or specific barriers to adherence (e.g. beliefs, depression) impact the

effectiveness of a PARTICS approach in these populations.

Hypothesis:
In these populations, a patient-empowered strategy of use of ICS triggered by patient use of short-acting beta-agonist (SABA) reliever for quick symptom relief ("rescue use") will reduce asthma exacerbations and improve other outcomes important to patients and the health care system.

BACKGROUND AND SIGNIFICANCE

Provide a brief paragraph summarizing prior experience important for understanding the proposed study and procedures.

Asthma imposes a significant burden on the US population in terms of morbidity, costs to society, individual suffering, loss of productivity and mortality. African Americans (AA) and Hispanic/Latinos (H/L) bear a disproportionate share of that morbidity. Despite introduction of national guidelines for asthma treatment, the gap between these groups and whites has been stable or widening. The need for pragmatic research to address the continuing burden is widely recognized. Patients use asthma reliever inhalers to provide immediate relief of symptoms. Controller inhalers (inhaled corticosteroids (ICS)) are intended to be used regularly to prevent symptoms and attacks. Guidelines suggest that they be used daily, on a fixed basis, in all but the mildest asthma. However, adherence by patients and implementation of evidence-based guideline recommendations by clinicians has been poor. Gap analysis suggests that it is difficult to improve adherence to the current recommendations without complex and resource-intensive interventions. Studies have examined symptom-activated use of ICS triggered by use of a reliever medication. We call this approach PARTICS – Patient Activated Reliever-Triggered Inhaled CorticoSteroid. Explanatory, non-real world studies suggest that PARTICS can produce up to 50% reductions in asthma attacks compared with usual care, while reducing ICS use by half or more. However, these studies have been performed in pre-selected populations, which represent less than 5% of patients with asthma. They have been done with repeated education and adherence checks in both the intervention and control arms throughout these studies.

We have consulted with AA and H/L patients, health care providers, leaders of professional societies, advocacy groups, health policy leaders, pharmacists, and pharmaceutical manufacturers. All groups have indicated that asthma decision making would be changed if we demonstrated that implementing PARTICS improves important asthma outcomes such as reducing rates of exacerbations. Together with our partners and stakeholders, we have designed a study to determine whether PARTICS can improve outcomes that are important to patients when superimposed on a background provider-educated standard care through the Asthma IQ system. We therefore propose a study entitled PREPARE: Patient Empowered Strategy to Reduce Asthma Morbidity in Highly Impacted Populations. We aim to determine whether a PARTICS strategy can reduce asthma morbidity in AA and H/L. Our primary outcome will be asthma exacerbations which have been shown to be important to patient and healthcare stakeholders. Our secondary outcomes will include additional outcomes important to patients (i.e. days lost from work or school, asthma control, & asthma quality of life). We have broad input and involvement from multiple stakeholder groups in study design, implementation, and commitments for dissemination. AA and H/L patients and their advocates have been involved and will continue to play a central role in all phases of the study.

RESEARCH DESIGN AND METHODS

Briefly describe study design and anticipated enrollment, i.e., number of subjects to be enrolled by researchers study-wide and by Partners researchers. Provide a brief summary of the eligibility criteria (for example, age range, gender, medical condition). Include any local site restrictions, for example, "Enrollment at Partners will be limited to adults although the sponsor's protocol is open to both children and adults."

VANGUARD:

"Vanguard" cohort of 36 patients (16 AA and 20 H/L) from four sites that represent our study sites' geographic, health system and practice size diversity; and patients that represent our anticipated enrollment of race, sex and age groups. We will enroll patients ages 18-75 based on the inclusion/exclusion criteria below. They will be enrolled in the Vanguard for 3 months. Self-identified African American and Hispanic/Latino patients at risk for exacerbations (e.g. on controller ICS with poor control, previous history of an exacerbation in previous 12 months or using ICS/LABA) will be identified from the clinical sites' through electronic health records and will be invited through their local provider's office to come for an enrollment visit either by letter, phone or may be approached during a clinic visit.

To better identify barriers to study participation, the Vanguard patients 32 of the 36 will be English speaking and enrolled 3:1 intervention (PARTICS) to non-intervention (enhanced usual care/Asthma IQ) so that we may observe how well the protocol and materials work. In addition to the 32 English speaking patients there will be 4 H/L Spanish speaking patients placed in the intervention group to be able to sufficiently test the intervention materials. This is a randomized, open-label trial in AAs and H/Ls 18 to 75 years old with asthma in which a standard of usual care, as requested by PCORI, is introduced (guided by the Asthma IQ educational program+ which we will call "provider
educated care"), and then patients are randomized to addition of a PARTICS strategy vs. continuing this standard of provider-educated enhanced usual care.

All patients (both PARTICS and control groups) will be asked to complete monthly questionnaires each month for using validated instruments to assess exacerbations, symptoms, medical visits primarily driven by asthma (visits, ED visits, and hospitalization) and medication use.

Each participant will be in the vanguard process for three months. After registration, vanguard participants will complete questionnaires at baseline (during registration) and each month for 3 months. The patients will also be called at 1 week, 6 weeks and at 3 months to ask them questions related to the enrollment process, questionnaires, their understanding of the instructions from the video and study coordinator.

VANGUARD INCLUSION CRITERIA

- Black or Hispanic based on self-identification (Hispanic if identify as both)
- Male and female, ages 18-75 years
- Ability to provide informed consent
- Clinical history consistent with asthma for > 1 year.
- Currently prescribed ICS as daily maintenance therapy. If prescribed ICS alone, then participant must also have an ACT score of 19 or less, **or** a history of one or more exacerbations in the past year that required patient report of systemic corticosteroid use.

VANGUARD EXCLUSION CRITERIA

- Life expectancy less than one year
- Use of systemic corticosteroid for an asthma exacerbation in the past month
- Known allergy to the ICS inhaler used in the study"
- Having COPD or other chronic lung disease other than asthma
- Regular oral steroids use daily or every other day for any reason---including asthma or other medical reasons
- Use of systemic corticosteroid for an asthma exacerbation in the past month (can wait and re-check eligibility after one month)
- Use of biologics (injections or infusion medicines)
- Another family member living in the same household already enrolled in study

FULL STUDY:

Differences from Vanguard: We anticipate enrolling 1200 patients. They will be enrolled for 15 months. The patients will be enrolled 1:1 intervention (PARTICS) to non-intervention (enhanced usual care/Asthma. The study will be conducted in up to 20 diverse health care settings across the country, many of which have been working with us on study development already. Patients **will not** be called at 1 week, 6 weeks and 12 weeks.

ELIGIBILITY CRITERIA

INCLUSION CRITERIA

- Black or Hispanic based on self-identification (Hispanic if identify as both)
- Male and female, ages 18-75 years
- Ability to provide informed consent
- Clinical history consistent with asthma for > 1 year.
- Prescribed ICS as daily maintenance therapy
- Participant must also have an ACT score of 19 or less, **or** a history of one or more exacerbations in the past year that required patient report of systemic corticosteroid use.

EXCLUSION CRITERIA

- Life expectancy less than one year
- Known allergy to the ICS inhaler used in the study
- Having COPD or other chronic lung disease other than asthma
- Regular oral steroids use daily or every other day for any reason--- including asthma or other medical reasons
- Use of systemic corticosteroid for an asthma exacerbation in the past month (can wait and re-check eligibility after one month)
- Use of biologics (injections or infusion medicines)
- Bronchial thermoplasty less than 6 months ago
- Another family member living in the same household already enrolled in study

Briefly describe study procedures. Include any local site restrictions, for example, "Subjects enrolled at Partners will not participate in the pharmacokinetic portion of the study." Describe study endpoints.

We will not be recruiting at any Partners institutions.

All sites will initially identify potentially eligible patients through specific searches of their EHR or data repository of EHR data designed to support research

Once a patient agrees to learn more about the study, the Research Coordinator will complete an eligibility questionnaire and registration process. The patient will then view an introduction/asthma education video. Once complete he/she will be consented either by the Research Coordinator or site PI.

After the consent process the patient will be randomized to either the Intervention (PARTICS) group or the control (Enhanced Usual Care) group and based on which group the patient is randomized to will view a second video which gives further instructions of what is expected throughout the study.

During the enrollment visit, we will ask patients to exhale into a machine that determines nitric oxide gas levels in their breath. We will also ask each participant if s/he agrees to have blood drawn. The blood draw is to determine Eosinophil counts which are known to be associated with response to Inhaled Corticosteroids. The test used will be a complete blood count with differential (CBC with differential). The amount of blood needed for this test is 3 mL, collected in a purple top tube. This will be the only blood draw for the participant throughout the study.

They will receive a pouch to hold the inhaler or inhalers (based on which group). They will receive a medication sheet to fill out the dose counter information when they receive a inhaler refill. If they are in the Intervention group they will receive a Velcro strap to hold the two inhalers together and an information card to give to providers explaining what they are doing with the inhalers (if needed).

The PARTICS group will receive their first QVAR and Propeller Health sensors to attach to their rescue inhaler and QVAR. The Usual Standard of Care group will receive a sensor for their Rescue inhaler only. Both groups will receive a hub for the sensors to be plugged in at home. The inhalers in this study will have dose counters. Study participants will self-report their rescue inhaler use in their monthly questionnaires using these dose counters. However, the Propeller system does not only work as a confirmatory method for counting doses (not just a counter). This is because the Propeller system also records the time at which the inhaler is being used; both the usual short-acting rescue inhaler plus the interventional ICS inhaler will have a Propeller Sensor. The purpose of measuring the time of inhalation is to assess whether or not participants are indeed using the interventional ICS inhaler at the same time as they use the short-acting rescue inhaler. For corroboration of self-reported doses we will cross-reference these data with the data from pharmacy fulfillment and TEVA supply data, in addition to the Propeller system.

They will then fill out questionnaires on the computer with the coordinator.

Full study difference: There will be no sensors provided for the inhalers. There will be one phone call by the site study coordinator within one month of enrollment to ask the patient about receiving the survey reminders and filling out the survey.

Study Questionnaires

Vanguard: The purpose of the Vanguard is to test whether the trial design and system is working appropriately. We will therefore ask participants Vanguard-specific questions which they will not be asked during the Full Study. Some of these questions address participants'

satisfaction with therapy (intervention only), assessment of enrollment process, assessment of receiving 1st inhaler (intervention only), assessment of monthly questionnaire process, etc.

Full study: We will ascertain the outcomes of this study through monthly questionnaires. Some of these questionnaires include the Asthma Exacerbation Questionnaire (AEQ), the Asthma Control Test (ACT), the Asthma APGAR, the Asthma Symptom Utility Index (ASUI), and others.

- Patients who fill out their monthly survey within six days of receiving their first reminder on day 26, will be entered into a lottery. They will have a chance to win one of three $100 prizes each month.
    - Sites located in Florida will not participate in the lottery due to state law.
- In addition, we will be implementing a few additions to focus on patient retention and engagement during the study. We will:
    - Send reminders to fill out their monthly survey via all methods of communication that the patient provides including text, email, and phone call.
    - send an appreciation card semi-annually to patients to keep in contact with them.
    - send a quarterly text message reminder (to all patients who have enabled text message reminders) about their treatment arm to encourage adherence to their medications and remind them about completing their monthly surveys.
    - send announcements via text message about winners of the lottery prizes (excluding any personal information), to help motivate patients to complete their surveys in a timely manner.

Study Outcomes and Statistical Analysis

A. Patient-centeredness of PREPARE outcomes

This study is designed to use real-world patient-reported outcomes (exacerbations, asthma control, quality of life, missed activities) that are of demonstrated importance to patients, providers, payers, and policy makers. Below we describe the patient-centeredness of our primary and major secondary outcomes.

B. Primary Outcome

Vanguard: We will be doing multiple assessments about the implementation and operationalization of the study processes. We will use descriptive statistics and qualitative analyses. Questionnaires administered to participants are included in the appendix.

Full study differences: We will be analyzing questionnaire data to address our hypotheses. There will be no assessments with regards to study processes as in the Vanguard phase.

Rate of asthma exacerbations per year is the primary outcome of this trial. It has been argued that exacerbations are the most important asthma outcome, because they constitute the greatest risk to patients, and are a cause of anxiety to patients and their families. All of our patient partners agreed that exacerbations have major impacts on their lives and would be interested in using PARTICS if it would prevent or significantly reduce exacerbations. In addition to their effects on patients, exacerbations result in a great stress on health care providers (Lane 2006, Skrepnek 2004, Andersson 2003) and are of high importance to payers and health care policy makers. Exacerbations increase the risk of asthma mortality (Jorgensen 2003) and generate the greatest cost to the health care system (Reddel 2009, Lane 2006). Asthma

exacerbations are recognized as a common clinical manifestation in patients with all levels of asthma severity (Pauwels 1997, O'Byrne 2001). National consensus guidelines have defined an asthma exacerbation as a worsening of asthma reported by the patient of a degree that requires treatment with corticosteroids (Revicki 1998).
The standardization of how we define asthma exacerbations was the focus of both an ERS/ATS Task Force (Reddell 2009) and a workshop sponsored by the NIH (Fuhlbrigge 2012).

Our primary outcome, the rate of asthma exacerbations per year, is defined as the number of exacerbations, emergency room visits, or hospitalizations requiring oral or parenteral corticosteroids, per patient per year. It will be captured by subject self-report via a monthly asthma exacerbations questionnaire (AEQ). Reports will be substantiated by verification in the EHR or direct patient interview. Multiple clinical trials demonstrate convergent validity with other measures of asthma-related health status (Busse 2011, Peters 2010, Lemanske 2010) and their responsiveness to intervention (O'Byrne 2005). We previously developed, tested, and used the AEQ as part of the BELT trial, in which we enrolled >1,000 AA patients. The AEQ is sensitive but not specific, meaning it overestimates the number of true exacerbations and therefore requires confirmation, but is not likely to miss exacerbations. Therefore, we will use the medical records or, if necessary, contact all patients whose form suggested an exacerbation to confirm. We will categorize these exacerbations as to whether they resulted in a hospitalization or emergency department visit. Using all sources of data available, an independent group of physicians (who are blinded about patient's randomized treatment) will adjudicate and classify all possible asthma exacerbation events to determine if an exacerbation is truly a primary endpoint event. All adjudications will be based on a document with pre- specified rules for adjudication.

C. Secondary Outcomes

1. Asthma Control: Asthma Control Test (ACT) score

Asthma control represents the degree to which impairment (impact of asthma on patient's daily life) is minimized and the goals of therapy are met. The National Asthma Education and Prevention Program's Expert Panel Report 3 (NAEPP 2007), of which Drs. Israel and Yawn were members or reviewers, emphasizes the importance of asthma control as a goal of therapy because of its relevance to patients and providers in the ongoing assessment of asthma. With the input of our stakeholders we will use the ACT (rather than the ACQ) for monthly outcome measures of asthma control. The Asthma Control Test (ACT) (described in D.III.8) measures asthma control— attainable only by patient report—and was developed to have low patient burden (Nathan 2004). Scores from the ACT allow providers to rapidly determine whether a patient's asthma is controlled or not (Nathan 2004). The ACT is self-reported and has been validated in multiple settings (office setting, mail, & by telephone) (D.III.8-Validation of Scales).

The ACT is easy to use, patient completed, and assesses the frequency of shortness of breath, use of rescue medications, the effect of asthma on daily functioning, and overall self-assessment of asthma control. The ACT has been evaluated in independent study population samples and can be self-administered in person or at home (Schatz 2007a), by telephone (Schatz 2007b) and by mail (Schatz 2007c). The ACT has been recommended by the NAEPP and the NIH Asthma outcome workshop (NAEPP 2007, Cloutier 2012) because of the extensive validation data for these tools, using the widest range of criterion and construct measures, including demonstration of responsiveness to therapy and a minimal clinically important difference (MCID). The MCID is defined as the smallest difference in a given score of interest which patients perceive as beneficial and which would support a change in the patient's management (Jaeschke 1989). The MCID for the ACT has been defined as 3 for individuals over time and between populations (Schatz 2009) and cut-off values for uncontrolled asthma:

ACT ≤ 19 (Nathan 2004), and "very poorly controlled" asthma: ACT ≤ 15 have been established. (Schatz 2006, Nathan 2004). Asthma APGAR will be used as a secondary assessment of control to see if the three questions with a shorter time reference and therefore less risk of recall bias can be used to replace the ACT. (Rank, MCP 2014).

2. Preference Based Quality of Life: Asthma Symptom Utility Index (ASUI)
The ideal outcome measure for any comparative effectiveness analysis captures the risks and benefits for each of the interventions from the patient's point of view. The use of a preference-based instrument, the Asthma Symptom Utility Index (ASUI), captures this important information (Revicki 1998). The measure is entirely patient experience focused. To develop this measure, patients were asked to assign a relative value to different health states. The ASUI has two important features that highlight its importance to patients: 1) the ASUI captures the tradeoff of the positive and negative aspects of interventions from the patient's point of view, and 2) the ASUI measures the severity and impact of asthma symptoms. For asthma, the type and severity of asthma symptoms can differ between individuals or differ in a given individual over time. In addition, certain symptoms may be more troublesome than others to patients, and certain treatments might be more or less desirable. Whereas a patient with severe asthma might not appear to improve in terms of having significant symptom free days, s/he might improve in the severity and or frequency of the symptoms, something that is not captured by symptom-free day scales. The ASUI is probably the symptom scale most frequently used in asthma studies including large multicenter clinical trials (Boushey 2005). The ASUI's psychometric properties are well documented and support the reliability and construct validity of the instrument, including internal consistency reliability and test-retest reliability. The minimum clinically important difference has been determined as 0.09 points (Bime 2012).

3. Days Lost from Work or School or Usual activities

As highlighted by our patient partners in our focus groups, days lost from work and school are a great concern for asthma patients. At the request of the patient partners, we have included this outcome measure. Days lost from work and school will be collected using a validated questionnaire developed and utilized as part of the National Health Interview Survey (NHIS 2014). If a patient does not work or go to school they are asked a question about days he/she was unable to carry out usual activities due to asthma. Our patient partners felt that this was a very important outcome that they would be interested in.

4. FeNO

Fractional exhaled nitric oxide (FeNO): Exhaled nitric oxide gas will be measured during the study visit. Asthma is an inflammatory disease of the lung. The PREPARE trial relies on the fact that in many cases asthmatic inflammation is of the eosinophilic (or Type 2) form of inflammation. Corticosteroids are particularly effective in targeting Type 2 inflammation. While inhaled corticosteroids (ICS) were initially thought to be a therapy for all asthmatics, studies now suggest that up to half of asthmatics may have non-type 2 inflammation and thus may be less responsive to ICS (Woodruff 2009). Thus, it is possible that PARTICS may be most beneficial for a particular group of patients – those with Type 2 mechanisms of inflammation.

5. Blood draw/Eosinophils

Peripheral blood eosinophils may identify asthmatics that are most responsive to Patient Activated Reliever-Triggered Inhaled CorticoSteroid (PARTICS). Eosinophil counts can be calculated by a complete blood count with differential. We will determine whether peripheral blood eosinophil count serves as an effect modifier of the relationship between treatment

(PARTICS vs. usual care) and the study's primary outcome (number of asthma exacerbations per year). We will stratify participants based on a pre-specified peripheral blood eosinophil count threshold of 300/uL. This threshold is based on a frequently-used cutoff for 'eosinophil-high' status in the anti-eosinophil therapy literature (Giannetti 2016).

Biostatistical Analysis, Statistical Design, and Sample Size

Vanguard data validation

The data transfer process will be tested in the Vanguard study. Data collected from Vanguard process will be transferred from the Patients Engaged Electronic Reporting System (PEERS) developed by the University of Colorado, Department of Family Medicine (CUDFM) to DCRI. The verification of data transfer integrity will be performed at DCRI according to DCRI SOP.

Unexpected data inconsistencies within and between data sources will also be examined and reported. It will help to determine if additional data queries or validation rules will need to be developed to ensure the data quality in the full study.

Randomization data from PEERS system will be compared with the original randomization scheme generated by DCRI to make sure the PEERS system randomization data match the randomization scheme created by DCRI. The randomization slots actually used by Vanguard patients will also be examined to make sure the randomization process works as planned in the Vanguard study.

Data collected through Vanguard process will be summarized by randomized treatment using appropriate descriptive statistics. Descriptive summaries of the continuous variables will be presented in terms of mean, standard deviation and percentiles (e.g., median, 25th and 75th percentiles), while discrete variables will be summarized in terms of frequencies and percentages. Due to the small sample size of the Vanguard study, no formal statistical tests will be performed.

Data report will focus on the Vanguard specific questions that survey about the study enrollment process, intervention process, monthly questionnaire process, and medication refill process. In addition, the screen failure data, patients' adherence barrier data from ASK-12, reasons of patients' drop-out or premature discontinuation, data on missed visits will also be carefully examined and reported. These data will help the study team to identify the barriers of patient enrollment, treatment compliance, and patient and physician adherence.

Full study differences: Formal statistical analyses will be performed.

1. Overview
Statistical analysis will be performed at the Statistical Data Coordinating Center at Duke Clinical Research Institute (DCRI). The study will use a randomized, parallel design to test the addition of PARTICS to provider-educated care as compared to continuation of provider-educated care. All major treatment comparisons between the randomized groups in this trial will be performed according to the principle of "intention- to-treat" (ITT); that is, subjects will be analyzed according to the treatment arm they were randomized to regardless of their compliance with the study medication.

Data collected in this study will be documented using summary tables with appropriate descriptive statistics for continuous variables and binary variables.

Annualized rates of count outcomes will be summarized using the annualized mean occurrence based on the Poisson model. In addition, survival curves will be constructed for all time to event endpoints using Kaplan-Meier methods.

Unless otherwise specified, the statistical analyses procedures for comparisons of the two groups will be as follows: 1) Two-sample t test or Kruskal-Wallis test for continuous parameters; 2) Chi-square test of independence for binary comparisons unless the number of events is less than 10, in which case Fisher's exact test will be used; 3) Cochran Mantel-Haenszel Modified Ridit Scores for non-time-to-event categorical variables with >2 categories (nominal variables will be compared using the General Association p-value; ordinal variables will be compared using the Row Mean Score p- value); 4) Andersen-Gill adaptation of Cox regression for time-to-event variables with more than one occurrence. 5) Log- rank test for first occurrence of time-to-event variables. All statistical tests and/or confidence intervals, as appropriate, will be performed at α=0.05 (2-sided) unless specified otherwise. SAS statistical software (version 9.1 or higher) will be used in analyses, unless otherwise noted.

2. Background Data and Baseline Characteristics:

Baseline demographic and clinical characteristics, including age, gender, socioeconomic status (SES), ethnic groups (Hispanic/Latino or African American), smoking status, BMI, medical history/comorbidities, asthma history, and asthma medication use (e.g., ICS/LABA use vs. ICS use) will be summarized for each randomized treatment arm of the study. Asthma exacerbations during the 12 months prior to randomization will also be reported.

In addition, data on patients' attitude towards ICS (by the Beliefs about Medications Questionnaire - BMQ), healthy literacy level (by S-TOFHLA questionnaire), depression level (by Patient Health Questionnaire—PHQ-2), treatment adherence likelihood (by ASK-12 questionnaire) will also be tabulated by randomized treatment groups.

Asthma exacerbations, Asthma Control Test (ACT) scores, lost days of work or schools within one month prior to randomization will also be reported using summary tables.

Only descriptive statistics will be reported for the baseline data. Continuous variables will be presented in terms of mean, standard deviation, and percentiles (e.g., median, 25th and 75th percentiles), while discrete variables will be summarized in terms of frequencies and percentages.

3. Treatment Compliance

Treatment Compliance will be monitored throughout the study. Numbers of patients non-compliant with treatment or crossing-over will be documented using counts and rates over time.

Sensitivity analyses will be performed for patients who have treatment cross- overs.

The primary analysis will be based on an Intention-to-treat analysis, but we will also conduct a Per Protocol analysis with available data.

4. Statistical Analysis for Primary Outcome

The primary aim of the study is to determine the impact of PARTICS on asthma outcomes in a minority population consisting of African American and Hispanic/Latino adults. The primary outcome of this study will be the intensity of asthma exacerbations during 15 months of follow-

up between those patients randomized to addition of PARTICS to provider-educated care vs. those who continue with provider-educated care alone.

Rate of asthma exacerbations per year will be reported for two treatment groups. Annualized rates of count outcomes will be summarized using the annualized mean occurrence based on the Poisson model.

Exacerbations rates during follow-up will be compared using the Andersen-Gill adaptation of time-to-event Cox proportional hazards model with robust standard errors to account for potential multiple occurrences of the outcome in each patient (Andersen Gill, 1982). This model was selected over the more commonly used time to first event Cox model for two reasons. First, we believe that total experience during follow-up matters more to patients than the onset of the first exacerbation. Second, the power is increased when multiple events can be included. The covariates in the primary comparison will include: study center (to account for any geographic variation in patterns of care), h/o exacerbations in the past year (y/n), on ICS/LABA prior to randomization (Y/N), race/ethnicity, smoking status (as defined for subgroups), age, BMI (body mass index), and gender since all may influence the rate of exacerbations or the response to corticosteroids. The primary effect will be based on the randomized treatment arm indicator variable.

Time from randomization to first asthma exacerbation will be compared using the log-rank test. In addition, survival curves will be constructed for this time-to-event endpoint using Kaplan-Meier method.

5. Secondary Outcome Analyses

Secondary outcome variables include asthma symptom utility index (ASUI), asthma control as measured by the Asthma Control Test, and the number of days lost from work or school. For outcomes measured as continuous variables, a linear mixed model will be employed to compare the treatment arms. The dependent variable will be change from the baseline value. The model will use data from all available assessments and the predictors (included as fixed- effects) will include randomized treatment arm, continuous time of assessment as a linear and quadratic term and the interactions of the treatment arm with the time variables. Independent random-effects will be included for intercept and time variables. The model will adjust for all the variables adjusted for in the primary analysis.

6. Subgroup Analysis

Subgroup analyses for the primary efficacy outcome will be performed on the ITT population in order to explore whether the treatment effect is consistent across subgroups. Our goal is to determine the impact of PARTICS on asthma exacerbations in two pre-specified main subgroups determined by 1) race/ethnic group (African American vs. Hispanic/Latino) and 2) smoking status [i.e., participants who are previous (>10 pack- years)/current (or within 1 year) smokers vs. those who have not smoked (in the past year and <10py)] 3) patients with high FeNO vs. low and 4) patients with high eosinophil counts vs. low. Based on our prior experience, about 50% of our population will be smokers or ex- smokers.

Subgroup analyses to evaluate variation in treatment effect will be performed on the basis of tests for interaction using the same Andersen-Gill version of the Cox proportional hazards model as used in the primary analysis. The model will be including terms for treatment arm, subgroup, and treatment by sub-group interaction and adjust for all variables included in the primary model. Additionally, treatment effects within each categorical subgroup will be examined

separately using analogous Andersen-Gill model. Event rates by treatment arm and hazard ratios with 95% confidence intervals will be reported for each subgroup.
Forest plots will be generated displaying the estimated hazard ratios and 95% confidence intervals for each subgroup will be presented. Variation in treatment effect will be assessed on the basis of tests for interaction in the Andersen-Gill version of the Cox proportional hazards model described above. Treatment effects estimated within each categorical subgroup will be considered exploratory/hypothesis generating. Thus, no adjustment for multiple testing will be employed.

Additional exploratory subgroup analyses will be performed investigating the effect of the following factors: 1) modality in which questionnaires have been returned; 2) patients' attitude towards ICS from the validated BMQ (skeptical (low necessity, high concerns), indifferent (low necessity, low concerns), ambivalent (high necessity, high concerns), accepting (high necessity, low concerns)); 3) presence of depressive symptoms (yes/no); 4) health literacy status (low or marginal versus high); and 5) patient adherence barriers from the validated ASK12 questions 1,2,3 and 11 related to measures of inconvenience, forgetting and cost.

Sample Size and Power Considerations

Sample size and power calculations were performed using PASS software (Hintze 2011), using the similarity of inference between the Andersen-Gill models and Poisson regression.

For the primary efficacy outcome, power calculations were based on an estimated primary event intensity of 0.4 per year (0.5 per 15 months) in the control arm (as seen in the BELT study), 15 months of follow-up for each individuals with an annualized rate of uniform loss to follow-up of 25% (31.25% in 15 months of follow-up) and a two-sided significance level of 0.05. With these assumptions, 1200 patients (600 per arm) yields 80% power to declare a reduction of 23.5% in the intensity of exacerbations as statistically significant.
Even if the event rate were lower at .35 we would still have 80% power to detect a 25% difference. This difference is clinically meaningful and is well within the 25-50% (and more likely 40-50%) (O'Byrne 2006, Rabe 2006, Buhl 2012, Papi 2013, Calhoun 2012)) reductions noted with such studies.

For subgroup analysis, using these same assumptions, with group size of 600 (300/arm), at a power level of 80% we would be able to detect an expected change of 32%, still well within the noted effects.

Power for secondary outcome comparisons were also calculated. Based on results observed in the BELT study, we expect the standard deviations in ASUI scores to be 0.23 in each arm. Thus, we will have 80% power to detect a difference of 0.04 in ASUI scores between treatment arms. Assuming standard deviations of 4.9 in each treatment arm on the ACT questions score, we will have 80% power to detect a difference of 0.96 in ACT scores.

Interim Analysis

It is anticipated that our independent safety officer will review the accumulating data at approximately 6-month intervals. Interim data analyses of the key safety and outcome data will be performed in a blinded fashion for each of these data reviews. The primary objective of these analyses will be to evaluate the accumulating data. Our independent safety officer will review the clinical outcome rates, patient recruitment, compliance with the study protocol, reasons and patterns of the missing data, adverse event rates and other factors that reflect the overall progress and integrity of the study.

Before each independent safety officer review session, a blinded summary safety data report will be provided to the safety officer. The extracted data files and the analysis programs for each independent safety officer report will be archived and maintained at the Statistical Data CC for the life of the study.

We will monitor the event rate as it accumulates in a blinded fashion to help us determine if we will achieve sufficient power. We will also review the baseline characteristics of enrolled participants to make sure we have enrolled the population defined in the protocol.

Addressing missing data

Every effort will be undertaken to limit premature discontinuations and ascertain completeness of data collection. Based on patient partner and patient advocate feedback, we are providing multiple methods of delivering the forms and multiple ways for participants to respond, including mail, email, telephone, text, smartphone app, website, and voice- response systems. We will also implement procedures designed to retain patients and increase responses. We will reimburse participants for completing forms with levels that our patient advisors felt would encourage completion. For any positive responses regarding exacerbations, we will call to verify and, where available, obtain medical records. We will also use the systems we used in our prior BELT study with AA participants to monitor missing data. Forms that are >10 days delayed result in attempts to re-contact the participant through all available consented modalities.

In concert with intent-to-treat principles, we will continue to attempt to obtain information on patients who failed to return questionnaires. Sites will have access to medical records, claims data and prescription refills. Thus, unless the patient has withdrawn consent, we will be able to continue collecting information on the primary outcome through these alternative means. We will obtain the following information for dropouts: 1) reason for dropping out; 2) primary determiner of dropout; 3) degree of participation. We will use a traditional consort diagram to track the randomized patients. Full sample size will be presented in all tables and figures with clear annotation of the numbers used for each analysis.

For the primary analysis (Andersen-Gill model) subjects discontinuing the study prematurely will be censored at the time of discontinuation. This approach might lead to biased results if discontinuation does not occur at random. Thus, two sensitivity analysis will be undertaken to examine the sensitivity of inference when data is missing at random and not at random: 1. Inverse probability weighting. In this approach, contribution of each subject to the risk set calculated at time t will be inversely weighted by the estimated probability of remaining uncensored up to time t. This probability will be estimated using a Cox proportional hazards model fitted to time to censoring with variables potentially prognostic of both, failure and censoring, both baseline and time- dependent (such as most frequent major protocol deviations, certain AEs etc.), entered as covariates. In order to reduce potentially high variability of the resulting treatment effect estimators due to sampling variability in weights, the weights will be "stabilized" by multiplication of probabilities of remaining uncensored up to time t estimated using baseline covariates only. 2. Pattern-mixture approach. As per Little 2012. we will assume that for participants who drop out, the hazard of an outcome deviates from that of participants who do not drop out by an offset--r1 for treatment and r0 for placebo. We will then explore the effect of this deviation on the findings for various choices of the offsets in the two study groups. If the treatment effect is qualitatively maintained for the range of offsets that are considered to be clinically plausible, then the findings will be considered to be robust.

In other analyses, missing data will handled by using multiple imputation. Ten imputed data sets will be generated with imputation methods based on the regression or Monte Carlo framework. Final results will be based on averages from the ten imputed data sets with appropriate

estimator employed of the variance. The variables included in the imputation model as covariates will be pre-specified.

For studies involving treatment or diagnosis, provide information about standard of care at Partners (e.g., BWH, MGH) and indicate how the study procedures differ from standard care. Provide information on available alternative treatments, procedures, or methods of diagnosis.

All participants in this study will be instructed to continue adhering to their usual controller therapy which follows the standard of care as assessed by their usual prescribing clinician. Participants will then be randomized to follow the PARTICS strategy or to continue using their usual controller therapy. The PARTICS strategy is different from standard of care in that it instructs participants to use inhaled corticosteroids every time that they use their rescue inhaler. The standard of care is for participants to use a fixed dose of inhaled corticosteroids regardless of their degree of symptoms. They are then supposed to treat increments in their asthma symptoms using their rescue inhalers, and not to change their dose of their regular, fixed dose, inhaled corticosteroids.

To reduce heterogeneity of the usual controller, standard of care therapy, all sites will be applying what we refer to as "provider-educated care". This will be standardized by implementation of the instructional component of the Asthma IQ system Primary Care Version (www.asthmaiq.org). We refer to this instructional component as 'enhanced usual care'.

This trial will not be testing an investigational new drug with the PARTICS strategy. Instead, it is testing a new way of using inhaled corticosteroids (new timing and frequency of use), which are a standard of care drug for asthma care.

Describe how risks to subjects are minimized, for example, by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk or by using procedures already being performed on the subject for diagnostic or treatment purposes.

Fractional exhaled nitric oxide (FeNO) testing: Exhaled nitric oxide gas will be measured during the study visit. This procedure involves exhaling into a device that measures FeNO. The associated risks are minimal. It is possible that a participant could become lightheaded from blowing into the machine, but this is uncommon since participants are instructed to not blow forcefully into the machine.

Blood eosinophil count: a blood draw of 3mL, or less than one teaspoon, will be taken from participants during the study visit, and a complete blood count with differential will be performed on the sample. The associated risks are minimal. It is possible that the participant will have some light bruising at the blood draw site, which will subside in a few days.

In terms of the intervention, we are adding inhaled corticosteroids to the study participants' usual rescue inhaler for those participants randomized to the PARTICS strategy.
All other changes in patient medications will be made by the patient's personal clinician. Thus, we are not introducing any study mandated changes in daily medications that would increase risk due to medication changes.

Describe explicitly the methods for ensuring the safety of subjects. Provide objective criteria for removing a subject from the study, for example, objective criteria for worsening disease/lack of

improvement and/or unacceptable adverse events. The inclusion of objective drop criteria is especially important in studies designed with placebo control groups.

We will not monitor non-asthma related adverse events due to the nature of this pragmatic trial. However, adverse events due to concurrent illnesses other than asthma may be grounds for termination from the trial if the illness is considered significant by the investigator or the patient's personal physician or other clinician or if the patient is no longer able to participate effectively in the study. Patients experiencing minor intercurrent illnesses may continue in the study (these may include acute rhinitis, sinusitis, upper respiratory infections, urinary tract infections, or gastroenteritis among others). Because this is a pragmatic trial, no restrictions on medications for treatment of these conditions will be made.

We will monitor asthma adverse events through questionnaire assessment of exacerbations, with confirmation through communication with the patient's primary site of asthma care. Due to the pragmatic nature of the study, no additional interventions will be provided unless the patient has an allergic reaction to the components of the ICS used for this study.

Unanticipated problems involving risks to subjects or others including adverse events will be reported to the PHRC in accordance with PHRC unanticipated problems reporting guidelines.

FORESEEABLE RISKS AND DISCOMFORTS

Provide a brief description of any foreseeable risks and discomforts to subjects. Include those related to drugs/devices/procedures being studied and/or administered/performed solely for research purposes. In addition, include psychosocial risks, and risks related to privacy and confidentiality. When applicable, describe risks to a developing fetus or nursing infant.

Risks associated with the use of inhaled corticosteroids

All subjects will have been on daily ICS maintenance therapy prior to enrollment in the study. Overall corticosteroid dosing may be increased in the intervention group, especially in the short term. However, data from efficacy studies of the PARTICS approach suggest that total inhaled corticosteroid dose will actually decrease as providers decrease the ICS dose due to improved patient control. Additionally, since we are targeting a group that has a high risk of exacerbation (1/3 or more based on our prior studies) for many subjects the total yearly dose of corticosteroids will be decreased even further due to avoidance of oral corticosteroid bursts resulting from the decreased rate of asthma exacerbations with PARTICS. All subjects will be informed that when taken at high doses for extended periods, ICS can produce hoarseness, sore throat, and thrush, as well as rarely cause adrenal gland suppression, weight gain, bruising of the skin, and diabetes. Subjects will be informed of these side effects and asked to see their physician if they experience bruising, acne, hoarseness, or fatigue. ICS use has also been associated with reduced growth velocity in children; but we will not enroll anyone under 18 years of age.

Pregnancy/fetus

Pregnancy is not a contraindication to asthma controller therapy, including ICS. Improved asthma control has been shown to be associated with improved pregnancy outcomes. We will advise all women to seek maternity care as soon as they are aware of the possibility of pregnancy and to inform their physician or nurse midwife of their participation in this study.

There is no foreseeable impact of this research on the fetus. To be in this study you must already be taking the same type of asthma maintenance medicine.

Risks associated with our study procedures: In addition to medical record review, and questionnaires throughout the study period, we will be measuring fractional exhaled nitric oxide (FeNO) gas and taking a 3mL blood sample during the enrollment visit. There are minimal associated risks with both—for the nitric oxide, it is possible that a participant could become lightheaded from blowing into a machine. For the blood draw, there could be a pinching sensation during the blood draw and light bruising afterwards.

Risks of asthma exacerbations:
Acute management of subjects' asthma is not changed or mandated by the study, and will be handled by the patient's chosen usual clinician in his/her usual manner. Training clinicians with the Asthma IQ instructional component as support for standardized provider educated care has been shown to improve asthma control and may be associated with decreased risk of exacerbations. The use of PARTICS (combined ICS+SABA) for acute symptom relief is intended to further reduce the risk of exacerbations and no data have been published to show that the use of combined acute relief medications increases exacerbation potential. Due to the pragmatic nature of the study, no additional interventions will be provided unless the patient has an allergic reaction to the components of the ICS used for this study. If such is the case both the patient and their care site will be notified to assure they have information on the exact medication to which the apparent allergic reaction occurred and the patient's participation in the study will be discontinued since no other options for a different type of ICS are available within the study.

Risk to Data Confidentiality:
Potential risks to data confidentiality will be mitigated by requirements for the de- identification of study data before secure transfer from the University of Colorado data collection site to Duke and by security protocols for the IHC patient-reported outcomes data capture systems. All users of the IHC system will be tracked and only provided access in a secure fashion following established UC-DFM Standard Operating Procedures for this process. The IHC system is an enterprise level system that handles multiple research and clinical data collection processes across thousands of individuals simultaneously. This project will be totally isolated from all other ongoing research activities. Patients will only have access to their personal information, questionnaires appropriate for their current research activities and the educational video(s) associated with their arm of the study. Site research staff will only have access to the patients enrolled by their site. AAFP NRN staff will have access to patient contact data for all patients, as well as reports indicating questionnaire status for each individual. The IHC system will automatically lock the monthly questionnaire for three weeks following completion by an individual assuring that we do not have duplicate completion of one month's questionnaire. The system will automatically remind individuals to complete questionnaires and unlock them at appropriate times. Missed questionnaires will not be locked until another questionnaire is completed. The risks of loss of confidentiality are minimal given the secure, central handling of these data.

EXPECTED BENEFITS

Describe both the expected benefits to individual subjects participating in the research and the importance of the knowledge that may reasonably be expected to result from the study. Provide a brief, realistic summary of potential benefits to subjects, for example, "It is hoped that the treatment will result in a partial reduction in tumor size in at least 25% of the enrolled subjects." Indicate how the results of the study will benefit future patients with the disease/condition being studied and/or society, e.g., through increased knowledge of human physiology or behavior, improved safety, or technological advances.

Expected benefits to the individual study participants

There might be no benefit to subjects from participating in this study. But we believe there may be a potential benefit to those participants randomized to the PARTICS arm but this is still unknown. The potential benefit would be decreased numbers of exacerbations (asthma episodes that require oral steroid bursts or hospitalizations) and possibly decreased symptoms and reduced need for extra asthma medications. It is also possible that implementation of the Asthma IQ training for standardized provider educated care may improve rates of asthma control in the participants randomized to the 'enhanced usual care' arm. This would thus benefit participants *in both arms* of the study.

Our proposed study seeks to inform a key health decision for people with asthma and clinicians who treat it-- should asthma patients' use, and providers prescribe, a controller medication to be used each time a reliever is used in order to reduce asthma exacerbations? The PREPARE trial can help with that decision by assessing the ability of PARTICS to reduce exacerbation occurrences, reduce days lost from school or work, and reduce the consumption of ICS – all outcomes of high importance to patients.

This health decision is particularly pertinent among AAs and H/Ls, who bear a disproportionate burden of asthma morbidity and are less likely to receive, choose, or be able to comply with guideline-driven care. If the study shows that the PARTICS approach reduces exacerbations and/or improves other outcomes important to patients, then this approach can easily be adopted by patients and their providers in the context of current care since it is intuitive and takes advantage of current patient-driven patterns of reliever inhaler use.

Importance of the knowledge that may result from the study

Asthma exacerbations are a substantial and important public health problem. PREPARE will teach us whether a PARTICS strategy can reduce asthma exacerbations in a real-world setting with high-risk populations as has been demonstrated in efficacy studies. It will also teach us whether the PARTICS approach can be implemented in health care systems that treat substantial numbers of minority patients. PARTICS-type strategies have been shown to significantly reduce exacerbations in carefully controlled efficacy studies by nearly 50%, but it's unclear patients will accept this strategy in real life outside the realm of an efficacy clinical trial. PREPARE will also teach us whether the rationale for the PARTICS approach is better understood and accepted by patients than current standards of care, and whether it can reduce potential barriers to asthma self-management, such as beliefs about medication, cost, forgetting medication, health literacy and depression. While our preliminary data suggests significant benefit of the PARTICS strategy across a diverse population, this trial will teach us whether particular subgroups of patients show a greater benefit from this approach.

Expected benefits to future patients

The potential for benefit to future patients with asthma is very significant as the PARTICS represents a new approach to asthma therapy. Current asthma controller therapy follows a rigid, provider-prescribed approach. This study will examine the potential benefits of a patient controlled approach added to typical use of daily controller medications. Gaps in adherence to controller asthma therapy are well documented. This trial may determine whether the PARTICS method can close this gap in care. Finally, the PARTICS approach may represent a benefit to African American and Hispanic/Latino adults, who bear a disproportionate burden of asthma.

EQUITABLE SELECTION OF SUBJECTS

The risks and benefits of the research must be fairly distributed among the populations that stand to benefit from it. No group of persons, for example, men, women, pregnant women, children,

and minorities, should be categorically excluded from the research without a good scientific or ethical reason to do so. Please provide the basis for concluding that the study population is representative of the population that stands to potentially benefit from this research.

Only African American and Hispanic/Latino adults ages 18 years and older with asthma will be enrolled in this study. These racial/ethnic groups are highly impacted with asthma morbidity; therefore our trial's aim is consistent with the PCORI's aim of reducing the burden of disease in highly impacted populations. No other racial/ethnic groups will be enrolled.
Women will be enrolled with no exclusion for pregnancy if determined acceptable by the woman's maternity care clinician(s). Statistics for studies of this type indicate that the percentage of women within the population to be enrolled will be approximately 60%. Children ages 18 to 21 will be included in this study. No safety concerns exist for this study among participants of this age group.

When people who do not speak English are excluded from participation in the research, provide the scientific rationale for doing so. Individuals who do not speak English should not be denied participation in research simply because it is inconvenient to translate the consent form in different languages and to have an interpreter present.

The PREPARE study focuses on minority populations, limiting its enrollment to African Americans/Blacks and Hispanic/Latinos. To ensure that literacy does not interfere with trial recruitment or data collection, all written trial material (English and Spanish) will be designed for a low-literacy audience. We will prepare video-based materials in English and Spanish for those who have trouble reading. English or Spanish videos will contain members of the group with which the patient self-identifies.

We will not recruit participants who do not speak either English or Spanish. This is to ensure that PREPARE clinical site staff and physicians can communicate with participants when a translator to languages other than English or Spanish is not present.

For guidance, refer to the following Partners policy:
Obtaining and Documenting Informed Consent of Subjects who do not Speak English
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Non-English_Speaking_Subjects.1.10.pdf

RECRUITMENT PROCEDURES

Explain in detail the specific methodology that will be used to recruit subjects. Specifically address how, when, where and by whom subjects will be identified and approached about participation. Include any specific recruitment methods used to enhance recruitment of women and minorities.

All sites will initially identify potentially eligible patients through specific searches of their EHR or data repository of EHR data designed to support research. Before contacting any patients, the provider or the practice Medical Director (who has been given permission to recruit on behalf of the practice) gives permission to contact the patient (this is the same for all contact scenarios). When an identified patient does not have a scheduled visit, the research coordinator will send

an informational letter about the study that would ask if he/she is interested in hearing more about the study. The research coordinator's information will be listed for the patient to call if interested. Patients who do have a scheduled visit will receive a phone call from the research coordinator giving a brief overview of the study and asking if they would like to hear more about the study during the clinic visit. If the research coordinator was unable to get in touch with the patient by phone the coordinator would approach the patient during the clinic visit (if approved by the medical provider. Patients who are sent a letter and don't respond will be will be called approximately 10 days after the letter is sent. Patients who are called and do not want to learn more about the study will be considered opt out unless they indicate they would like to be contacted a later date. Patients who are seen in the clinic and do not want to participate, will be considered opt out unless indicating that they would like to be contacted at a later date.

Provide details of remuneration, when applicable. Even when subjects may derive medical benefit from participation, it is often the case that extra hospital visits, meals at the hospital, parking fees or other inconveniences will result in additional out-of-pocket expenses related to study participation. Investigators may wish to consider providing reimbursement for such expenses when funding is available

Vanguard: Remuneration will be by ClinCard which cash will be added to when a patient enrolls ($50), and when each questionnaire is completed ($20 X 3 = $60), each phone call ($20 X 3 = $60), if the patient receives additional monthly charges for using their smartphone or computer to answer the questions ($5 X 3 = $15), and when the patient returns the sensor ($20). Total for enrollment, answering all questionnaires, completing all phone calls, and returning the sensor is $205.

Full Study differences: When each questionnaire is completed ($20 X 15 = $300), $20 for single blood draw at enrollment, and if the patient receives additional monthly charges for using their smartphone or computer to answer the questions ($5 X 15 = $75). Total amount possible in the full study is $445 ($50 + $300 +$20+ $75) after enrollment and completion of all questionnaires.

- Patients who fill out their monthly survey within six days of receiving their first reminder on day 26, will be entered into a lottery. They will have a chance to win one of three $100 prizes each month. Sites located in Florida will not participate in the lottery due to state restrictions.

For guidance, refer to the following Partners policies:

Recruitment of Research Subjects
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Recruitment_Of_Research_Subjects.pdf

Guidelines for Advertisements for Recruiting Subjects
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Guidelines_For_Advertisements.1.11.pdf

Remuneration for Research Subjects
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Remuneration_for_Research_Subjects.pdf

CONSENT PROCEDURES

Explain in detail how, when, where, and by whom consent is obtained, and the timing of consent (i.e., how long subjects will be given to consider participation). For most studies involving more than minimal risk and all studies involving investigational drugs/devices, a licensed physician investigator must obtain informed consent. When subjects are to be enrolled from among the investigators' own patients, describe how the potential for coercion will be avoided.

Vanguard:

Informed consent form will be uniform throughout the sites except as required by a site's IRB; Partners will serve as the central IRB. Two approaches to completion of informed consent will be available to facilitate enrollment. Most patients will be consented in person by a Research Coordinator at each site. There will be the opportunity to complete the consent process online via Skype or FaceTime with a designated Research Staff person at BWH. The study consent form will be embedded in the PEERS data collection system, The consent component of the PEERS system has been used for multiple previous studies. Data collected prior to consent is anonymous and remains so if the patient decides not to participate in the study. Once the patient provides consent not only is that information stored but selected responses from prior to the consent process can be used to supplement the intake survey data.

Documentation of this process will be required, the subject will e-sign the informed consent document or sign a paper consent form if required by the local IRB. Electronic signatures will be maintained by the PEERS system and documentation of each enrolled participant's consent will be provided to the AAFP NRN by each site obtaining it. Paper consent forms will be maintained at the site as part of the subject's research records (which may be separate from their medical records) as well as a copy provided to the AAFP NRN and to the participant. No participant will be enrolled without documentation of informed consent and no waivers of this process will be sought or granted due to the use of the addition of a medication in the intervention. The PEERS system has been used for many studies with online consent approved by over 15 IRBs across the country.

Participants not found to be eligible will be requested to voluntarily and anonymously provide their gender, race and ethnicity for tracking purposes. For eligible patients the consent process will include the aims of the study, the data collection, follow-up requirements, and all potential risks and benefits of the study. A research coordinator will be available to discuss the study with the subject or answer questions either in person or through two way video. A BWH research coordinator will facilitate the video-based consent process. We anticipate that only a minority of informed consent processes will be obtained through video-conference with the BWH research coordinator,

During the consent process the patient must agree to the Propeller User Agreement so that the inhaler sensor/s can be registered with Propeller Health to collect inhaler usage data that will be downloaded to the PEERS data system. If the patient does not agree to the Propeller User Agreement or to having the sensor put on the inhaler/s, they will not be entered into the Vanguard portion of the study.

Patients enrolled in the Vanguard portion of the study will not be eligible to participate in the Full study.

Full study:

Difference: The only difference with the consent process from the Vanguard is that the patients will not be receiving sensors to go on the inhaler/s to track usage and will therefore not have to agree to the Propeller User Agreement.

There will be no video-conference consent.

NOTE: When subjects are unable to give consent due to age (minors) or impaired decision-making capacity, complete the forms for Research Involving Children as Subjects of Research and/or Research Involving Individuals with Impaired Decision-making Capacity, available on the New Submissions page on the PHRC website:
https://partnershealthcare.sharepoint.com/sites/phrmApply/aieipa/irb

For guidance, refer to the following Partners policy:
Informed Consent of Research Subjects:
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Informed_Consent_of_Research_Subjects.pdf

DATA AND SAFETY MONITORING

Describe the plan for monitoring the data to ensure the safety of subjects. The plan should include a brief description of (1) the safety and/or efficacy data that will be reviewed; (2) the planned frequency of review; and (3) who will be responsible for this review and for determining whether the research should be altered or stopped. Include a brief description of any stopping rules for the study, when appropriate. Depending upon the risk, size and complexity of the study, the investigator, an expert group, an independent Data and Safety Monitoring Board (DSMB) or others might be assigned primary responsibility for this monitoring activity.

NOTE: Regardless of data and safety monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for protecting the rights, safety, and welfare of subjects under his/her care.

We will appoint an independent safety officer from the Division of Pulmonary and Critical Care Medicine from Brigham and Women's Hospital who has no other role in the PREPARE Trial. This independent safety officer will be presented data in a blinded manner, and review safety data twice annually.

All patients will be trained to recognize adverse events associated with their asthma control. They will receive written instructions on the use of their medications. If a subject experiences an adverse event, s/he will contact his/her local physician. The local physician will evaluate the subject, either on□the phone and/or in person if needed, and determine the nature and severity of the event, and whether or not it is related to the study procedures or medications. The site physician will ensure appropriate site documentation, patient management, and follow up to resolution. We will prepare annual reports for IRB approval as needed.

We will not monitor non-asthma related adverse events due to the nature of this pragmatic trial. However, adverse events due to concurrent illnesses other than asthma may be grounds for termination from the trial if the illness is considered significant by the investigator or the patient's

personal physician or other clinician or if the patient is no longer able to participate effectively in the study.

We will monitor asthma adverse events through questionnaire assessments of exacerbations, with confirmation through communication with the patient's primary site of asthma care. Due to the pragmatic nature of the study, no additional interventions will be provided unless the patient has an allergic reaction to the components of the ICS used for this study.

Unanticipated problems involving risks to patients or others including adverse events will be reported to the PHRC in accordance with PHRC unanticipated problems reporting guidelines.

Describe the plan to be followed by the Principal Investigator/study staff for review of adverse events experienced by subjects under his/her care, and when applicable, for review of sponsor safety reports and DSMB reports. Describe the plan for reporting adverse events to the sponsor and the Partners' IRB and, when applicable, for submitting sponsor safety reports and DSMB reports to the Partners' IRBs. When the investigator is also the sponsor of the IND/IDE, include the plan for reporting of adverse events to the FDA and, when applicable, to investigators at other sites.

NOTE: In addition to the adverse event reporting requirements of the sponsor, the principal investigator must follow the Partners Human Research Committee guidelines for Adverse Event Reporting

We will not monitor non-asthma related adverse events due to the nature of this pragmatic trial. However, adverse events due to concurrent illnesses other than asthma may be grounds for termination from the trial if the illness is considered significant by the investigator or the patient's personal physician or other clinician or if the patient is no longer able to participate effectively in the study. We will monitor asthma adverse events through questionnaire assessments of exacerbations, but due to the pragmatic nature of the study, no additional interventions will be provided unless the patient has an allergic reaction to the components of the ICS used for this study. Unanticipated problems involving risks to patients or others including adverse events will be reported to the PHRC in accordance with PHRC unanticipated problems reporting guidelines.

MONITORING AND QUALITY ASSURANCE

Describe the plan to be followed by the principal investigator/study staff to monitor and assure the validity and integrity of the data and adherence to the IRB-approved protocol. Specify who will be responsible for monitoring, and the planned frequency of monitoring. For example, specify who will review the accuracy and completeness of case report form entries, source documents, and informed consent.

NOTE: Regardless of monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for ensuring that the study is conducted at his/her investigative site in accordance with the IRB-approved protocol, and applicable regulations and requirements of the IRB.

We will use the PEERS system to capture data electronically. PEERS will be programmed such that patient intake, baseline and monthly questionnaire data is required to be completed prior to

advancing to the next section. Thus, patients who complete the consent, enrollment, baseline and monthly data collection processes should have complete data. All outcome data will be selected from radio button or pick list questions and thus data will be codified at the time of capture. These sites will be monitored by a daily PEERS report to the central AAFP NRN staff. If a site appears to be struggling with recruitment the AAFP NRN staff may make a site visit to see if they can assist with rethinking the recruitment process.

Access to the data collection system and database will be strictly controlled and well documented. Personnel at the University of Colorado Department of Family Medicine (UCDFM) and the Statisticians at Duke providing statistical analysis will have no right to delete or change data. Only the site and central site users will have this ability. Data cleaning will be done by automatic or manually created queries to the site users who will need to confirm and change data in response. All the data changes will be tracked by the system and stored in a database audit trail which can be accessed as needed.

PEERS is hosted in the UCDFM data center (which also serves as the HIPAA compliant data center for all DARTNet activities.) This center is secured environment with 24 hour police monitoring, password controlled entry that is monitored as well as both local and central police alerts for open/ajar doors. The entire center is located behind the University of Colorado Palo Alto firewall with advanced intrusion detection software and monthly remote server auditing for security. The data environment is located behind a second, research/clinical firewall maintained by the UCDFM informatics staff. All data transmissions for end users are encrypted. The UCDFM maintains daily incremental back-ups, weekly system images and monthly full file level back-ups. Off-site and cloud back-up storage is maintained with a 12 month rotation system.

For guidance, refer to the following Partners policies:

Data and Safety Monitoring Plans and Quality Assurance
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/DSMP_in_Human_Subjects_Research.pdf

Reporting Unanticipated Problems (including Adverse Events)
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Reporting_Unanticipated_Problems_including_Adverse_Events.pdf

PRIVACY AND CONFIDENTIALITY

Describe methods used to protect the privacy of subjects and maintain confidentiality of data collected. This typically includes such practices as substituting codes for names and/or medical record numbers; removing face sheets or other identifiers from completed surveys/questionnaires; proper disposal of printed computer data; limited access to study data; use of password-protected computer databases; training for research staff on the importance of confidentiality of data, and storing research records in a secure location.

NOTE: Additional measures, such as obtaining a Certificate of Confidentiality, should be considered and are strongly encouraged when the research involves the collection of sensitive data, such as sexual, criminal or illegal behaviors.

Potential risks to data confidentiality will be mitigated by requirements for the de- identification of study data before secure transfer from the University of Colorado data collection site to Duke

and by security protocols for the IHC patient-reported outcomes data capture systems. All users of the IHC system will be tracked and only provided access in a secure fashion following established UC-DFM Standard Operating Procedures for this process. The IHC system is an enterprise level system that handles multiple research and clinical data collection processes across thousands of individuals simultaneously. This project will be totally isolated from all other ongoing research activities. Patients will only have access to their personal information, questionnaires appropriate for their current research activities and the educational video(s) associated with their arm of the study. Site research staff will only have access to the patients enrolled by their site. AAFP NRN staff will have access to patient contact data for all patients, as well as reports indicating questionnaire status for each individual. The IHC system will automatically lock the monthly questionnaire for three weeks following completion by an individual assuring that we do not have duplicate completion of one month's questionnaire. The system will automatically remind individuals to complete questionnaires and unlock them at appropriate times. Missed questionnaires will not be locked until another questionnaire is completed. The risks of loss of confidentiality are minimal given the secure, central handling of these data.

Support for our PEERS/IHC data repositories will be provided by the UCDFM, an AAFP NRN partner, and will meet all HIPAA privacy and security requirements including strong passwords and secure URLs. These data will then be transferred into the study database at the U of Colorado Denver Department of Family Medicine. The data to be collected and the manner of de-identification will be discussed with the enrolled patients as part of the informed consent process.

SENDING SPECIMENS/DATA TO RESEARCH COLLABORATORS OUTSIDE PARTNERS

Specimens or data collected by Partners investigators will be sent to research collaborators outside Partners, indicate to whom specimens/data will be sent, what information will be sent, and whether the specimens/data will contain identifiers that could be used by the outside collaborators to link the specimens/data to individual subjects.

Data on all patients will be collected and entered into the Patient Engaged Electronic Reporting System- PEERS study database. Data will be de-identified before being sent to the statisticians at Duke University for analysis.

Specifically address whether specimens/data will be stored at collaborating sites outside Partners for future use not described in the protocol. Include whether subjects can withdraw their specimens/data, and how they would do so. When appropriate, submit documentation of IRB approval from the recipient institution.

As noted above, all data will be stored using the IHC repository managed by University of Colorado and later transferred securely to Duke.

RECEIVING SPECIMENS/DATA FROM RESEARCH COLLABORATORS OUTSIDE PARTNERS

When specimens or data collected by research collaborators outside Partners will be sent to Partners investigators, indicate from where the specimens/data will be obtained and whether the specimens/data will contain identifiers that could be used by Partners investigators to link the specimens/data to individual subjects. When appropriate, submit documentation of IRB

approval and a copy of the IRB-approved consent form from the institution where the specimens/data were collected.

All data collected and stored at the data repository at UCDFM would be coming from outside Partners.